October 6, 2005

Timothy Adams, Ph.D.
Technical Contact
International Association of Color Manufacturers
HPV Committee
1620 I Street, N.W.
Suite 925
Washington, DC 20006

Dear Dr. Adams:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Sulfanilic Acids posted on the ChemRTK HPV Challenge Program Web site on August 13, 2004. I commend the International Association of Color Manufacturers for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Association advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: N. Patel
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Sulfanilic Acid and 4-Amino-5-methoxy-*o*-toluenesulfonic acid

Summary of EPA Comments

The sponsor, The International Association of Color Manufacturers/HPV Committee, submitted a test plan and robust summaries to EPA for sulfanilic acid (CAS No. 121-57-3) and 4-amino-5-methoxy-*o*-toluenesulfonic acid (*p*-cresidine sulfonic acid; CAS No. 6471-78-9), dated July 9, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 13, 2004. The submission also includes information on FD&C Red No. 40, FD&C Yellow No. 5 and FD&C Yellow No. 6 as supporting chemicals.

EPA has reviewed this submission and has reached the following conclusions:

1. General. In the cover letter, on the cover pages of the test plan and robust summaries, and on page 2 of the test plan the CAS number (6471-78-3) given for *p*-cresidine sulfonic acid should be 6471-78-9.

2. Category Definition and Justification. Sulfanilic acid and *p*-cresidine sulfonic acid have similar structures and physicochemical and environmental fate properties and are reasonably considered together. Additional information is needed to support use of the azo dye data.

3. Physicochemical Properties. Adequate data were provided for sulfanilic acid for the purposes of the HPV Challenge Program. The submitter needs to provide measured melting point and water solubility data for *p*-cresidine sulfonic acid.

4. Environmental Fate. Adequate data are provided for all environmental fate endpoints for the purposes of the HPV Challenge Program.

5. Health Effects. With sufficient added support for the supporting chemical approach the submitted data on the precursor azo dyes can be considered adequate for all endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

6. Ecological Effects. Because all ecological effects studies are from secondary sources and lack details, they are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide adequate acute toxicity data on fish, invertebrates, and green algae.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Sulfanilic Acid and 4-Amino-5-methoxy-
***o*-toluenesulfonic Acid Challenge Submission**

Category Definition

Although two chemicals technically do not constitute a category, the two submitted chemicals are sufficiently similar (structure, physicochemical properties, environmental fate) to be considered in one submission.

Supporting Chemicals Justification

The submitter provided data on three azo dyes to address human health effects because these dyes metabolize *in vivo* to the sponsored substances. The low toxicity of the azo dyes, with supporting evidence describing their metabolic processes, suggests that the proposed approach could be adequate for the purposes of the HPV Challenge Program. However, as presented, there are some uncertainties and deficiencies, and a lack of logical flow among the various presentations of data.

Because no pharmacokinetic data were submitted to describe the rate of metabolism of the azo dye supporting chemicals, it is difficult to attribute clinical observations to the azo dyes or identified metabolites. The test plan discussion of the azo dyes omits rates and materials balance information, percent conversion, and whether all metabolites were identified. The submitter needs to better address these facets of azo dye metabolism.

A direct comparison of the metabolic behavior of the sponsored substances is not possible because metabolic fate data are given for sulfanilic acid but not *p*-cresidine sulfonic acid. If metabolism data are not available for the latter, the test plan needs to include either data on a structurally similar substance, or (given the potential metabolic reactivity of the methyl and methoxy substituents of *p*-cresidine sulfonic acid) an explanation of the relevance or nonrelevance of the structural differences. A statement as to why the toxicity of sulfanilic acids administered orally will parallel that of the same compounds when liberated from azo dyes in the intestine is also needed.

Robust summaries for the supporting metabolism studies of azo dyes and sulfanilic acids need to be added to the submission.

The pyrazolone structure on page 2 is missing the second ring nitrogen.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

Adequate data are provided for boiling point, vapor pressure, and partition coefficient endpoints for the purposes of the HPV Challenge Program. The measured data for melting point and water solubility for sulfanilic acid are also adequate.

Melting Point. The estimated melting point of *p*-cresidine sulfonic acid is inadequate for the purposes of the HPV Challenge Program. The use of estimated values introduces uncertainties that then become magnified in modeling applications. The submitter needs to provide a measured value for *p*-cresidine sulfonic acid.

Water Solubility. The estimated value for *p*-cresidine sulfonic acid is not adequate for the purposes of the HPV Challenge Program as the measured and estimated values for sulfanilic acid are not very close and the analog data found by EPA for *p*-cresidine sulfonic acid are rather scattered. The submitter needs to provide a measured value for *p*-cresidine sulfonic acid.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Adequate data are provided for all endpoints for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

With sufficient added support for the supporting chemical approach (see Supporting Chemicals Justification), the submitted data on the precursor azo dyes for all endpoints can be considered adequate for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

Ecological Effects (fish, invertebrates, algae)

The submitted data are inadequate because they are from secondary sources, lack method details and are of unknown reliability. The submitter needs to provide adequate measured acute toxicity data for all three ecological endpoints (OECD TGs 201, 202 and 203).

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. In two acute toxicity summaries of mouse studies by oral and intraperitoneal routes of administration (Gaunt, et al, 1967) the mouse weights are given as 20-25 kg instead of 20-25 g.

Genetic toxicity (mutagenicity). In the guideline study for sulfanilic acid given a Klimisch reliability code of 1 (Chung, et al, 1981), the purity of the test substance needs to be provided.

Genetic toxicity (chromosomal aberrations). For the rodent micronucleus test with FD&C yellow No. 6 (Westmoreland and Gatehouse, 1991), the number of animals and the positive controls used need to be identified.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.